DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

DEC 9 2004

CBER-05-006

# WARNING LETTER

**CERTIFIED MAIL**
**RETURN RECEIPT REQUESTED**

Howard Pien
President and Chief Executive Officer
Chiron Corporation
4560 Horton Street
Emeryville, California 94608-2916

Dear Mr. Pien:

The Food and Drug Administration (FDA) conducted an inspection of Evans Vaccines, an affiliate of Chiron Corporation, Gaskill Road, Speke, Liverpool L24 9GR, United Kingdom, between October 10 and October 15, 2004. During the inspection, FDA investigators documented deviations from current good manufacturing practice (CGMP) in the manufacture of Influenza Virus Vaccine, Fluvirin® (Fluvirin), including the bulk monovalent blend pools and trivalent bulk batches. These deviations from CGMP include the applicable requirements of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and Title 21, Code of Federal Regulations, (21 CFR) Parts 210, 211, and 600-680. These violations of CGMP render your product adulterated under Section 501(a)(2)(B) of the FD&C Act and not safe, pure, and potent under Section 351(a) of the Public Health Service Act (PHS Act).

At the close of the inspection, FDA issued a Form FDA 483, Inspectional Observations, that described a number of significant objectionable conditions relating to the facility's compliance with CGMP. Significant deviations in the manufacture of Fluvirin observed during the inspection include, but are not limited to, the following:

1. Your facility's quality control unit failed to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated; the quality control unit also failed to investigate thoroughly any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications [21 CFR 211.22 and 211.192] For example:

a) The quality control unit's investigation of Fluvirin sterility failures (Fluvirin Sterility Failure Investigation Report #R/0198/04, October 9, 2004) concluded that [redacted] fumigation of your facility's formulation areas on May 17, 2004 "was successful" as confirmed by your ongoing environmental monitoring program. Yet environmental data from April 2004 through September 2004 for formulation rooms [redacted] and [redacted] indicate continued alert and action level excursions for gram negative organisms, including but not limited to *Serratia spp.*

b) The Fluvirin sterility failure investigation conducted by the quality control unit failed to include and address the bulk sterility failure of B/Jiangsu monovalent blend pool #[redacted].

c) The Fluvirin sterility failure investigation conducted by the quality control unit failed to address the fact that numerous monovalent blend pools (over 50%) used from March 2004 through October 2004 exceeded your firm's bioburden alert level ([redacted] cfu/ml).

d) The quality control unit did not thoroughly investigate the environmental monitoring excursions during filling for Fluvirin lots [redacted] and [redacted]. The non-conformance reports were limited to review of the filling activity for each specified lot. There was no investigation in these non-conformance reports of aseptic filling area environmental monitoring excursions that occurred for other lots between September 2004 and October 2004, and which subsequently resulted in the rejection of the lots.

2. Your firm failed to follow written procedures applicable to the function of the quality control unit. [21 CFR 211.22(d)] For example:

a) Your firm's standard operating procedure (SOP) M198 "Sterility Investigation Reports" requires that the facility initiate a Non-Conformance Report (NCR) upon the determination of a valid positive sterility test (sterility test failure). Your firm's SOP SCP009 "Non Conformance Reporting" requires that "the identifier of a Non-Conformance must initiate a Non-Conformance report form as soon as reasonably possible, [redacted] where detection of the Non-Conformance was highlighted" (emphasis in original). These SOPs were not followed in that:

i) Individual NCR reports were not initiated, completed and approved for the nine lots of Fluvirin [redacted] that failed sterility testing.

ii) The non-conforming events associated with the nine lots of Fluvirin that failed sterility testing were not investigated using an NCR in a thorough and timely manner with corrective and preventive actions assigned and implemented.

b) Your firm's SOP MDP-0024 "Routine Monitoring and Review of Adverse Events to Identify Safety Signals" requires that the facility conduct a batch review if certain criteria relating to adverse drug experiences are satisfied. This SOP was not followed in that there is no documentation that batch record reviews were conducted by the quality control unit for adverse event reports received for at least twenty-two batches of Fluvirin manufactured in the 2004 campaign, where one or more criteria for review were satisfied.

3. Your firm failed to establish and follow scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity. [21 CFR 211.160(a) and (b)] For example, the facility did not present an established, scientifically sound justification, rationale, and/or procedure for the sampling and testing of additional filled vials to confirm the extent of the unsatisfactory sterility test results on batches of Fluvirin.

4. Your firm failed to establish and follow appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile and to assure that such procedures include validation of any sterilization process. [21 CFR 211.113(b)] For example, the process simulation media fills performed to demonstrate aseptic processing during Fluvirin production are inappropriate in that your procedures simulate separately the [redacted] final vial filling, which is not representative of the entire aseptic process. In addition, SOP SCP029 "General Procedure for Routine Monitoring of Aseptic Manufacturing Processes by Process Simulation Utilizing Sterile Media Fills" requires performance and documentation, during media fills, of all interventions performed during actual aseptic filling operations. Your facility did not follow this SOP in that all interventions were not documented for the simulation fills of monovalent and trivalent blending.

5. Your firm failed to establish and follow written procedures, and to justify any deviation from written procedures, for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. [21 CFR 211.100(a) and (b)] For example, SOP M201 "Identification of a Micro-organism" requires that all microorganisms be speciated upon isolation. Between January and September 2004, only 20% of the microbial isolates had been identified and speciated.

6. Your firm failed to establish an adequate system for monitoring environmental conditions of aseptic processing areas. [21 CFR 211.42(c)(10)(iv)] For example, routine viable air sampling does not encompass aseptic activities including the times and locations where the critical operations are performed.

7. Your firm failed to establish separate or defined areas or other control systems for aseptic processing operations to prevent contamination or mixups. [21 CFR 211.42(c)(10) and 600.11(a)] For example, formulation rooms [redacted] and [redacted] do not meet

manufacturing needs and prevent contamination, due to the equipment configurations within the Class [redacted] area, in that the airflow, above the critical area where multiple aseptic connections are made, is obstructed by the operators when making the connections.

8. Your firm failed to establish and follow written procedures to assure the cleaning and maintenance of equipment used in the manufacture, processing, packing, or holding of a drug product. [21 CFR 211.67(b) and 600.11(b)] For example, cleaning validation for the clean-in-place (CIP) process Vessel [redacted] which is utilized in the aseptic formulation of trivalent bulk influenza vaccine, did not include an assessment of the spray ball coverage for the vessel. The spray ball is used for cleaning product contact equipment. In addition, the study did not include swab sampling of the product transfer lines.

Additionally, significant deviations in manufacture of your bulk drug substance were observed during the inspection. These deviations cause your bulk drug substance to be adulterated within the meaning of Section 502(a)(2)(B) of the FD&C Act and not safe, pure, and potent under Section 351(a) of the PHS Act. Specific areas of concern include, but are not limited to:

INVESTIGATION OF FAILURES

1. There is no indication that failures are fully investigated or that you extended investigations to other batches as appropriate. For example:

   a) Numerous Fluvirin monovalent blend pools (over 50%) manufactured between March 2004 and October 2004 and used in the formulation of trivalent batches manufactured for the 2004 Fluvirin Campaign, greatly exceeded the bioburden alert level of [redacted] cfu/ml. Although non-conformance reports were completed, your firm did not conduct a thorough investigation into the root cause of the increased bioburden levels. Your firm failed to implement corrective and preventive actions.

   b) Your firm used numerous cultures of live virus inoculum that exceeded the bioburden alert level of less than [redacted] cfu/ml in the inoculation of eggs during the 2004 Fluvirin campaign. A thorough investigation into the root cause of the increased bioburden levels was not conducted. In addition, corrective and preventive actions were not implemented.

CLEANING AND MAINTENANCE OF EQUIPMENT

2. Appropriate validation studies have not been conducted for critical processes. For example, validation for the manual cleaning of the upper and lower rotor assemblies of equipment used for zonal centrifugation operations have not been performed.

3. There is no indication that prior to August 2004 there were periodic preventive maintenance programs or procedures to prevent malfunctions or contamination for the [redacted] tanks. In addition, the cleaning validation did not include an assessment of the spray ball coverage for the tanks.

PRODUCTION AND PROCESS CONTROLS

4. Batch production records are inadequate in that many of the [redacted] tanks are not traceable throughout manufacturing operations for specific lots of product.

All of the above deficiencies are indicative of your quality control unit's inability to fulfill its responsibility to assure the identity, strength, quality, and purity of your drug product [21 CFR 211.22].

We acknowledge receipt of your written response dated November 13, 2004, regarding the inspectional observations listed on the Form FDA 483. Corrective actions addressed in your response may be referenced in your response to this letter; however, we believe that your response did not provide sufficient detail to allow FDA to assess fully the adequacy of the corrective actions. Our evaluation of your response follows, and is numbered to correspond to the items listed on the Form FDA 483:

Observations 1, 4, 5 and 7
We acknowledge your commitments to enhance your Quality System Improvement Program to develop more robust processes in your Quality Systems and to strengthen the organizational structure of your quality control unit. As described in the FDA Form 483 and this letter, however, Chiron has not performed adequate investigations into deviations as required by applicable FDA regulations. Please describe in detail how Chiron will attain GMP compliance with regard to deviation investigations by, among other things, taking into account other failures or discrepancies that may be related, and then using all of the relevant information to conduct a root cause analysis to ensure that adequate steps are taken for the evaluation of product impact, deviation investigations, and the implementation of effective corrective and preventive actions.

Observation 1H
We acknowledge your commitment to hire a Chief Microbiologist in order to improve the scientific basis in the design of studies to aid in your investigations. Please describe in detail how Chiron will ensure that the studies you conduct are scientifically sound and justified and conducted according to appropriate procedures, specifications, standards, and sampling plans.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as management to assure that your establishment is in compliance with the provisions of the FD&C Act, PHS Act, and applicable federal regulations. Federal agencies are

advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

Please notify us in writing, within 15 working days of receipt of this letter, of the steps you have taken or will take to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to correct these deviations promptly may result in regulatory action without further notice. Such actions may include license suspension and/or revocation. Your reply should be sent to James S. Cohen, J.D., Acting Director, Office of Compliance and Biologics Quality, U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448. If you have any questions regarding this letter, please contact Ms. Mary Malarkey, Director, Division of Case Management, at (301) 827-6201.

Sincerely,

David K. Elder
Director
Office of Enforcement

cc: John Lambert
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